REMARKC/ARGUMENTS

Claims 17-20 and 22-33 are pending. Claims 1-16 and 21 are cancelled. Claim 17 is amended. Claims 25-33 are added.

Support for the amendments can be found on pages 2-3 and page 13, line 17, through page 15, line 19, and the Examples on pages 16-20. Support for claim 33 can be found in original claim 21.

Applicants thank Examiners Guzo and Makar for a meeting with the undersigned on April 19, 2007. The Examiners indicated that submission of a certified English translation of provisional application 60/463,311 would overcome some prior art rejections. Some proposed amendments were discussed and which are submitted here. The Examiners indicated that the rejections under 35 U.S.C. 102 would be likely withdrawn in view of these amendments.

Applicants claim priority to provisional application 60/463,311. Applicants have now submitted an English translation of this application, now abandoned. Applicants request that priority to 4/17/2003, the filing date of application 60/463,311, be granted.

The claimed invention is directed to a method for promoting expression of LKLF/KLF2 gene, comprising administering inhibitors of the mevalonic and metabolic pathway to a subject suffering from a blood vessel disorder. LKLF/KLF2 gene is expressed from vascular endothelial cells and is important for blood vessel stabilization. Thus, LKLF/KLF2 gene is useful for treatment of diseases associated with blood vessel disorders (see pages 2-3).

Claims 1-4, 6-7, 9-12, 14-15, 17-20, and 22-23 are rejected under 35 U.S.C. 102(a) in view of Parmer, *JBC*, 280(29):26714-19 (2005). Claims 5, 13, and 21 are rejected under 35 U.S.C. 103(a) over Parmer, in view of Maejima. Claims 8, 16, and 24 are rejected under 35 U.S.C. 103(a) over Parmer, in view of Hausding.

The Parmer reference was published on July 22, 2005. The present application was filed on September 29, 2005, as a national stage application of PCT/JP04/05316 which was filed on April 14, 2004. Therefore, Parmer is not prior art for this application. Applicants request these rejections be withdrawn.

Claims 1-4, 8-12, 16-20, and 24 are rejected under 35 U.S.C. 102(b) in view of Hausding, *Brit. J. Pharmacol.*, 131:553-561 (2000).

Hausding investigates involvement of Ras and Rho proteins in the induction of a nitric oxide synthesis (NOS II), which can have a beneficial effect, such as *antimicrobial*, *antiatherogenic* or *antiapoptotic* (page 553). Inappropriate induction of NOS II can have detrimental consequences, such as cellular injury in *arthritis*, *colitis*, or *septic shock* (page 553, left-hand col.). Hausding describes using HMG-CoA reducatse inhibitors (e.g., statins) and TcdB in cell assays. Hausding also describes geranylgeranyltransferase inhibitors and farnesyltransferase inhibitors (page 554). However, Hausding does not suggest administering the disclosed inhibitors to a subject suffering from a *blood vessel disorder* and, specifically, blood vessel disorders of claims 25-31.

Applicants request that the rejection be withdrawn.

Claims 1-5 are rejected under 35 U.S.C. 102(b/e) over each of Fujikawa, US 5,011,930; Ohara, US 5,284,953; Fujikawa, US 5,854,259; Fujikawa, US 5,854,259; Muramatsu, US 6,465,477; Tanizawa, US 2004/0018235; Oida US 2005/0148626; Aoki, 2006/0111437; or Nakagawa, US 2005/0256141.

Claims 1-5 have been cancelled. These references do not disclose a method as claimed because they do not describe administering HMG-CoA inhibitors to a subject suffering from blood vessel disorders and, specifically, diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity

pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid.

Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(b/e) in view of Aoki, US 7,022,713.

US 7,022,713 was filed on February 19, 2004, and issued on April 14, 2006. The present application, which is a 371 of PCT application filed on April 14, 2004, claims priority to US provisional application 60/463,311 filed on April 17, 2003. A certified English translation is attached and is also being filed in the provisional file. Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Oida, US 2005/0148626.

US 2005/0148626, published on July 7, 2005, is a national stage application of PCT/JP03/04626, filed on April 11, 2003, that was not published in English. Therefore, US 2005/0148626 does not have 102(e) date. The 102(a) date is July 7, 2005, based on the publication date of the application. As stated above, the present application is a 371 of a PCT application filed on April 14, 2004. Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(e) over Yokoyama, US 2006/0217352.

US 2006/0217352 was filed on June 22, 2005 and was published on September 28, 2006. It claims priority to provisional application 60/665,390 filed on March 28, 2005. As

stated above, the present application is a 371 of a PCT application filed on April 14, 2004. Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(e) over Nakagawa, US 2005/0256141.

US 2005/025614, published on November 17, 2005, is a national stage application of PCT/JP03/03995, filed on March 28, 2003, but was not published in English. Therefore, US 2005/025614 does not have 102(e) date. The 102(a) date is July 7, 2005, based on the publication date of the application. As stated above, the present application is a 371 of a PCT application filed on April 14, 2004. Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(b/e) over Fujikawa, US 5,854,259.

Fujikawa describes administering HMG-CoA reductase inhibitors for the reduction of hyperlipidemia, hyperlipoproteinemia or athrosclerosis. Fujikawa does not suggest administering such inhibitors to a subject suffering from blood vessel disorders and, specifically, blood vessel disorders of claims 25-31. Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(b/e) over Morikawa, US 2003/0195167.

Morikawa describes a method for suppressing expression of PTX3 gene by administering an effective amount of HMG-CoA reductase inhibitors to a subject suffering from an autoimmune disease (e.g., rheumatoid arthritis) (page 1, claims 1 and 6). Morikawa does not suggest administering such inhibitors to a subject suffering from blood vessel

disorders and, specifically, blood vessel disorders of claims 25-31. Applicants request that the rejection be withdrawn.

Claims 1, 6-7, 9, 14-15, 17, and 22-23 Claims 9-13 and 17-21 are rejected under 35 U.S.C. 102(b) over Lerner, *JBC*, 270(45):26770-73 (1995).

Lerner describes disrupting oncogenic Ras processing and signaling with a geranylgeranyltransferase inhibitor (page 26770). Lerner also describes fernesyltransferase inhibitors (page 26770). However, Lerner only discloses fernesylation of Ras with regard to its *oncogenic* activity (page 26770, left-hand col.). Lerner discloses that Ras is a substrate for FTase and serves as a target for designing inhibitors of this enzyme with a potential anticancer activity (page 26771, right-hand col., last paragraph). Lerner uses human Burkitt lymphoma cells for selecting inhibitors having anticancer activity. Lerner does not suggest that the inhibitors promote expression of LKLF/KLF2 gene and can be administered to a subject having blood vessel disorders as is claimed in the present application. Applicants request that the rejection be withdrawn.

Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of US 5,011,930; claim 1 of US 5,284,953; claims 1-4 of US 5,854,259; claims 1-15 of US 6,465,477; 1-7 of US 2004/0018235; or 7-8 of US 2006-0111437.

Claims 1-5 have been cancelled. Applicants request that the rejection be withdrawn.

Claims 1-5, 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of US 5,856,336.

The claimed method is directed to promoting expression LKLF/KLF2 gene in a subject having a blood vessel disorder.

Claim 2 of the '336 patent is directed to a method for reducing an elevation of lipids in the bloodstream (e.g., hyperlipidemia, hyperlipoproteinemia) or reducing arthrosclerosis (plaque formation) by administering HMG-CoA inhibitors.

The '336 patent does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder and, specifically, diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid. Claims 1-5 have been cancelled. Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of US 7,022,713.

The claimed method is directed to promoting expression LKLF/KLF2 gene by administering the claimed inhibitors to a subject having a blood vessel disorder.

Claims 1-2 of the '713 patent are directed to a method for treating hypertriglyceridemia by administering HMG-CoA inhibitors.

The '713 patent does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder and, specifically, diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid.

Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of US 2003/0195167.

The claimed method is directed to promoting expression LKLF/KLF2 gene by administering the claimed inhibitors to a subject having a blood vessel disorder.

Claims 1-7 US 2003/0195167 are directed to methods for suppressing expression of PTX3 gene and treating a subject suffering from an autoimmune disease (e.g., rheumatoid arthritis) by administering HMG-CoA inhibitors.

US 2003/0195167 does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder and, specifically, diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid.

Applicants request that the rejection be withdrawn.

Claims 1-5, 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of US 5,872,130.

The claimed method is directed to promoting expression LKLF/KLF2 gene by administering the claimed inhibitors to a subject having a blood vessel disorder.

Claim 5 of the '130 patent is directed to a method for reducing an elevation of lipids in the bloodstream (e.g., hyperlipidemia, hyperlipoproteinemia) or reducing arthrosclerosis (plaque formation) by administering HMG-CoA inhibitors.

The '130 patent does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder and, specifically, diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid. Claims 1-5 have been cancelled. Applicants request that the rejection be withdrawn.

Claims 1-5, 9-13, and 17-21 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 7-13 of US 2005/0148626.

The claimed method is directed to promoting expression LKLF/KLF2 gene by administering the claimed inhibitors to a subject having a blood vessel disorder.

Claims 7-13 of US 2005/0148626 are directed to a method for treating a subject suffering from a coagulation disorder and sepsis by administering HMG-CoA inhibitors.

US 2005/0148626 does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder such as diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid.

Applicants request that the rejection be withdrawn.

Claims 9-13 and 17-21 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of US 2006/0217352.

The claimed method is directed to promoting expression LKLF/KLF2 gene by administering the claimed inhibitors to a subject having a blood vessel disorder.

The claims of US 2005/0148626 are directed to a method for treating thrombosis by administering HMG-CoA inhibitors.

US 2005/0148626 does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder such as diabetes, angina, myocardial infarction, hemoendothelial functional disorder, post-PTCA restenosis, hypertensivity pneumonitis, intestinal pneumonia, airway constriction, airway obstruction, eyeground bleeding, cerebrovascular dementia, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and hemorrhoid.

Applicants request that the rejection be withdrawn.

Claims 1-5, 9-13, and 17-21 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of US 2005/0256141 (application 10/504,851).

Application 10/504,851 is abandoned. Applicants request that the rejection be withdrawn.

Claims 1-5, 9-13, and 17-21 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-17 of US 2006/0257474.

The claimed method is directed to promoting expression LKLF/KLF2 gene by administering the claimed inhibitors to a subject having a blood vessel disorder.

The claims of US 2006/0257474 are directed to a method for treating a glomerular disease (kidney lesion) by administering HMG-CoA inhibitors.

US 2006/0257474does not suggest administering the inhibitors to a subject suffering from a blood vessel disorder.

Applicants request that the rejection be withdrawn.

Claims 2, 9, and 18 are rejected under 35 U.S.C. 112, second paragraph.

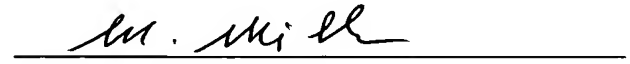
The term "lactone derivative" is widely known in the art. A hydroxy acid is both an alcohol and an acid. In those cases where a five- or six-membered ring can be formed, intramolecular esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield *a cyclic ester known as a lactone* (see Boyd, Organic Chemistry, 6th ed, Farrell ed., Prentice Hall, Englewood Cliffs, NJ 07632, 1992). The lactone of a carboxylic acid is a heterocyclic ring having as ring members the group –C(=O)-)-; all remaining ring members are carbon atoms, and carbon atoms bonded to either the carbon or oxygen or –C(=O)O- group may not themselves be double bonded to chalcon (see Class Definition for Class 520, USPTO Classification at http://www.uspto.gov/go/classification/uspc520/defs520.htm, 2 pages). Thus, "lactone derivative" of a carboxylic acid is a well known and well defined term.

Applicants request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Marina I. Miller, Ph.D.
Attorney of Record
Registration No. 59,091

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
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Prefac
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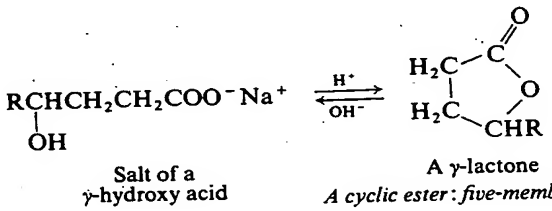
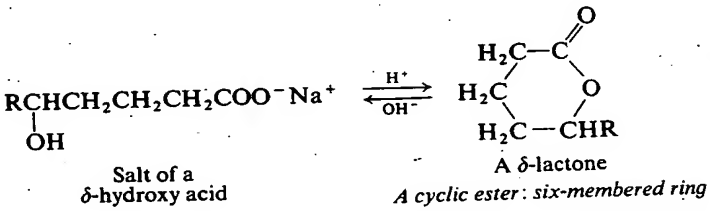
As was mentioned earlier, esterification using aromatic acid chlorides, ArCOCl, is often carried out in the presence of base (the Schotten–Baumann technique, Sec. 20.8).

Problem 20.11 When benzoic acid is esterified by methanol in the presence of a little sulfuric acid, the final reaction mixture contains five substances: benzoic acid, methanol, water, methyl benzoate, sulfuric acid. Outline a procedure for the separation of the pure ester.

A hydroxy acid is both alcohol and acid. In those cases where a five- or six-membered ring can be formed, *intramolecular* esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a **lactone**. Treatment with base (actually hydrolysis of an ester) rapidly opens the lactone ring.



Salt of a γ-hydroxy acid — A γ-lactone: *A cyclic ester: five-membered ring*



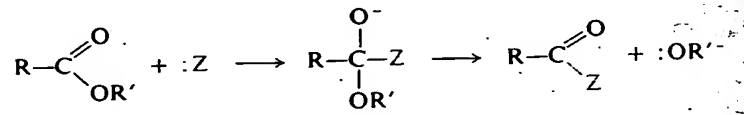
Salt of a δ-hydroxy acid — A δ-lactone: *A cyclic ester: six-membered ring*

to give the open-chain salt. We shall encounter lactones again in our study of carbohydrates (Sec. 34.8).

Problem 20.12 Suggest a likely structure for the product formed by heating each of these acids: (a) *Lactic acid*, $CH_3CHOHCOOH$, gives *lactide*, $C_6H_8O_4$. (b) 10-Hydroxydecanoic acid gives a material of high molecular weight (1000–9000).

20.16 Reactions of esters

Esters undergo the nucleophilic substitution that is typical of carboxylic acid derivatives. Attack occurs at the electron-deficient carbonyl carbon, and results in the replacement of the —OR′ group by —OH, —OR″, or $—NH_2$:



$:Z = :OH^-, \quad :OR''^-, \quad :NH_3$

CLASS 520, SYNTHETIC RESINS OR NATURAL RUBBERS -- PART OF THE CLASS 520 SERIES

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SECTION I - CLASS DEFINITION

The lactone of a carboxylic acid is a heterocyclic ring having as ring members the group -C(=O)-O- ; all remaining ring members are carbon atoms, and the carbon atoms bonded to either the carbon or oxygen or the -C(=O)O- group may not themselves be double bonded to chalcogen (i.e., oxygen, sulfur, selenium, or tellurium). J. A carboxylic acid salt denotes the structure $-C(=O)-O-^{\ominus}X^{\oplus}$, where X is a cation and ionic bonding exists between the cation, X, and the -C(=O)O- group. The carbon of the -C(=O)O- group may be bonded to: (1) hydrogen; (2) a carbon atom that is not double bonded to sulfur, selenium, or tellurium, or triple bonded to nitrogen; or (3) $[-C(=O)-]_n$, where n is an integer. In the above definitions of carboxylic acids and their derivations, certain derivations may technically fit into more than one derivative grouping. A lactone, for example, is a species of an ester, and a lactam is a species of an amide.